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(71) Applicant: RESEARCH CORPORATION TECHNOLOGIES, INC. [US/US]; Suite 606, 101 North Wilmot Road, Tucson, AZ 85711-3335 (US).

(72) Inventor: KOHN, Harold; 4012 Aberdeen Way, Houston, TX 77025 (US).

(74) Agents: DIGIGILIO, Frank, S. et al.; Scully, Scott, Murphy &amp; Presser, 400 Garden City Plaza, Garden City, NY 11530 (US).

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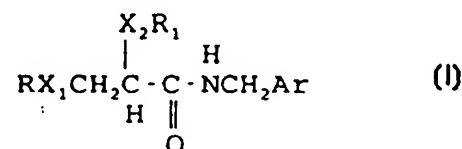
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(54) Title: PROPIONAMIDE DERIVATIVES AND THEIR USE AS ANTICONVULSANTS

## (57) Abstract

The present invention is directed to a compound useful as an anticonvulsant. The compound has formula (I):  $X_2R_1$  when  $X_2=S$ ,  $HX_2R_1$  when  $X_2=S$ .



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## PROPRIONAMIDE DERIVATIVES AND THEIR USE AS ANTICONVULSANTS

1

5

FIELD OF THE INVENTION.

10 The present invention relates to novel compounds useful as anticonvulsants.

BACKGROUND OF THE INVENTION

15 The predominant application of anticonvulsant drugs is the control and prevention of seizures associated with epilepsy or related central nervous system disorders. Epilepsy refers to many types of recurrent seizures produced by paroxysmal excessive neuronal discharges in the brain; the two  
20 main generalized seizures are petit mal, which is associated with myoclonic jerks, akinetic seizures, transient loss of consciousness, but without convulsion; and grand mal which manifests in a continuous series of seizures and convulsions with  
25 loss of consciousness.

The mainstay of treatment for such disorders has been long-term and consistent administration of anticonvulsant drugs. Most drugs in use presumably exert their action on neurons, glial cells or both of  
30 the central nervous system. The majority of these

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1 compounds are characterized by the presence of at  
least one amide unit and one or more benzene rings  
that are present as a phenyl group or as part of a  
cyclic system.

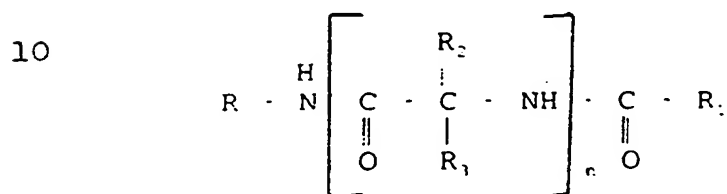
5 Much attention has been focused upon the  
development of anticonvulsant drugs. As a result many  
such drugs have been prepared. For example, the  
hydantoins, such as phenytoin, are useful in the  
control of generalized seizures and all forms of  
10 partial seizures. The oxazolidinediones, such as  
trimethadione and paramethadione, are used in the  
treatment of nonconvulsive seizures. Phenacemide, a  
phenylacetylurea, is one of the anticonvulsants  
employed today. However recently, much attention has  
15 been focused on diazepines and piperazines. For  
example, US Patent Nos. 4,002,764 and 4,178,378 to  
Allgeier, et al. disclose esterified diazepine  
derivatives useful in the treatment of epilepsy and  
other nervous disorders. US Patent No. 3,887,543 to  
20 Nakanishi, et al. describes a thieno [2,3-e][1,4]  
diazepine compound also having anticonvulsant activity  
and other depressant activity. US Patent No. 4,  
209,516 to Heckendorn, et al. relates to triazole  
derivatives which exhibit anticonvulsant activity and  
25 are useful in the treatment of epilepsy and conditions  
of tension and agitation. US Patent No. 4,372,974 to  
Fish, et al. discloses a pharmaceutical formulation  
containing an aliphatic amino acid compound in which  
the carboxylic acid and primary amine are separated by  
30 three or four units. Administration of these compounds

-3-

1 in an acid pH range is useful in the treatment of  
convulsion disorders and also possess anxiolytic and  
sedative properties.

US Patent No. 5,378,729 to Kohn, et al.

5 discloses compounds and pharmaceutical compositions  
having central nervous system (CNS) activity which are  
useful in the treatment of epilepsy and other CNS  
disorders having the formula:



wherein

15 R is hydrogen, lower alkyl, lower alkenyl,  
lower alkynyl, aryl, aryl lower alkyl, heterocyclic,  
heterocyclic lower alkyl, lower alkyl heterocyclic,  
lower cycloalkyl, lower cycloalkyl lower alkyl, and R  
20 is unsubstituted or substituted with at least one  
electron withdrawing group or electron donating group;

R<sub>1</sub> is hydrogen, lower alkyl, lower alkenyl,  
lower alkynyl, aryl lower alkyl, aryl, heterocyclic  
lower alkyl, heterocyclic, lower cycloalkyl, lower  
25 cycloalkyl lower alkyl, each unsubstituted or  
substituted with an electron donating group or an  
electron withdrawing group;

R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, lower  
alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower  
30 alkyl, heterocyclic, heterocyclic lower alkyl, lower

35

1 alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl  
lower alkyl, or Z-Y, wherein  $R_2$  and  $R_3$  may be  
unsubstituted or substituted with at least one  
electron withdrawing group or electron donating group:

5 Z is O, S, S(O),  $NR_4$ ,  $PR_4$  or chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower  
alkyl, lower alkenyl, lower alkynyl, halo,  
heterocyclic or heterocyclic lower alkyl, and Y may be  
unsubstituted or substituted with an electron donating  
10 group or an electron withdrawing group, provided that  
when Y is halo, Z is a chemical bond; or

ZY taken together is  $NR_4NR_5R_7$ ,  $NR_4OR_5$ ,  $ONR_5R_7$ ,  
 $OPR_4R_5$ ,  $PR_4OR_5$ ,  $SNR_4R_7$ ,  $NR_4SR_7$ ,  $SPR_4R_7$ ,  $PR_4SR_7$ ,  $NR_4PR_5R_6$ ,

15  $PR_4NR_5R_7$ ,  $NR_4CR_5$ ,  $SCR_5$ ,  $NR_4COR_5$ , or  $SC-OR_5$ ;  

$$\begin{array}{cccc} \parallel & \parallel & \parallel & \parallel \\ O & O & O & O \end{array}$$

$R_4$ ,  $R_5$  and  $R_6$  are independently hydrogen,  
lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or  
20 lower alkynyl, wherein  $R_4$ ,  $R_5$ , and  $R_6$  may be  
unsubstituted or substituted with an electron  
withdrawing group or an electron donating group;

$R_7$  is  $R_5$ ,  $COOR_5$  or  $COR_5$ ;

$R_8$  is hydrogen, lower alkyl or aryl lower  
25 alkyl and the aryl or alkyl group may be unsubstituted  
or substituted with an electron withdrawing group or  
an electron donating group;

n is 1-4 and

a is 1-3.

30

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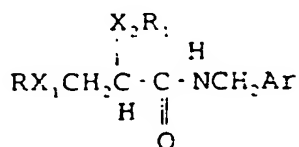


1           Unfortunately, despite the many available  
 pharmacotherapeutic agents for the treatment of  
 epilepsy, a significant percentage of the population  
 with epilepsy still suffers from this malady.  
 5   Moreover, none of the drugs presently available are  
 capable of achieving total seizure control and most  
 have disturbing side effects. Clearly, current  
 therapy has failed to fully control these debilitating  
 diseases.

10           These shortcomings of these drugs on the  
 market has prompted the present inventor to find new  
 drugs having anticonvulsant properties. The present  
 invention provides novel compounds exhibiting CNS  
 activity, particularly anticonvulsant activity, which  
 15   are useful for treating epilepsy and other CNS  
 disorders.

#### SUMMARY OF THE INVENTION

20           Accordingly, the present invention is  
 directed to propionamides of the formula:



25

I

or pharmaceutically acceptable salts thereof  
 wherein

30

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1           Ar is aryl which is unsubstituted or  
substituted with at least one electron donating group  
or electron withdrawing group;

          R and R<sub>1</sub> are independently lower alkyl,  
5   aryl, aryl lower alkyl, lower cycloalkyl or lower  
cycloalkyl lower alkyl, wherein R and R<sub>1</sub> groups are  
independently unsubstituted or substituted with at  
least one electron donating group or electron  
withdrawing group;

10           X<sub>1</sub> and X<sub>2</sub> are independently O, S or NR<sub>1</sub>; and  
R<sub>2</sub> is hydrogen or lower alkyl.

          The present invention is also directed to  
pharmaceutical compositions containing  
pharmaceutically effective amounts of the propion-  
15 amides of the present invention. In addition, the  
present invention is also directed to a method of  
treating central nervous system disorders in animals,  
especially mammals, in need of such treatment  
comprising administering thereto an anticonvulsant  
20 effective amount of the propionamide of the present  
invention. The administration of an effective amount  
of the present compounds in their pharmaceutically  
acceptable form provides an excellent regime for the  
treatment of epilepsy, nervous anxiety, psychosis,  
25 insomnia, and other central nervous disorders.

#### DETAILED DESCRIPTION OF THE PRESENT INVENTION

          As used herein, the term "lower alkyl", when  
30 used alone or in combination with other groups, refers

1 to alkyl groups containing 1-6 carbon atoms, which may  
be straight-chained or branched. These groups include  
methyl, ethyl, propyl, isopropyl, butyl, isobutyl,  
tertiary butyl, sec-butyl, amyl, pentyl, isopentyl,  
5 hexyl, and the like. The preferred alkyl group is  
methyl.

The term "aryl", when used alone or in  
combination with other groups, refers to an aromatic  
group which contains no heteroatoms and which contains  
10 from 6 up to 18 ring carbon atoms and up to a total of  
25 carbon atoms. The aryl group may be monocyclic,  
bicyclic, or tricyclic. If more than 1 ring is  
present, the rings are fused. The aryl groups also  
include polynuclear aromatics. By polynuclear  
15 aromatics, it is meant to encompass bicyclic and  
tricyclic fused aromatic ring systems containing from  
10-18 ring carbon atoms and up to a total of 25 carbon  
atoms. Examples of aryl include phenyl, naphthyl  
(both  $\alpha$  and  $\beta$ ), anthracenyl, phenanthrenyl, azulenyl,  
20 and the like. The preferred aryl group is phenyl.

The "aryl lower alkyl" group refers to a  
lower alkyl group, as defined herein, bridging an aryl  
group, as defined herein, to the main chain. Examples  
include benzyl, phenethyl, phenpropyl, phenisopropyl  
25 phenbutyl, diphenylmethyl, 1,1-diphenylethyl, 1,2-  
diphenylethyl, and the like.

The term "lower cycloalkyl" when used alone  
or in combination with other groups is a cycloalkyl  
group containing 3-6 ring carbon atoms and up to total  
30 of 10 carbon atoms. The cycloalkyl group is

1 monocyclic and is completely saturated. Examples  
include cyclopropyl, cyclobutyl, cyclopentyl and  
cyclohexyl and the like. Substituted cycloalkyl  
groups include both the cis and trans forms.

5 "Lower cycloalkyl lower alkyl" when used  
herein denotes a lower alkyl group, as defined herein,  
bridging a lower cycloalkyl group as defined herein to  
the main chain. Examples include cyclopropylmethyl,  
cyclopentylmethyl, cyclohexylmethyl, cyclobutylpropyl,  
10 cyclohexylmethyl, cyclobutylmethyl, and the like.

The terms "electron withdrawing groups" and  
"electron donating groups" refer to the ability of a  
substituent to withdraw or donate electrons relative  
to that of hydrogen if the hydrogen atom occupied the  
15 same position in the molecule. These terms are well  
understood by one skilled in the art and are discussed  
in Advanced Organic Chemistry, by J. March, 4th Ed.  
John Wiley and Sons, New York, NY pp 15-18 (1992), and  
the discussion therein is incorporated by reference.  
20 Examples of electron withdrawing groups include halo,  
especially fluoro, bromo, chloro, iodo, and the like;  
nitro; carboxy; formyl; lower alkanoyl; carboxyamido;  
triloweralkylamino; aryl; trifluoromethyl; aryl lower  
alkanoyl; lower carbalkoxy; and the like. Examples of  
25 electron donating groups include such groups as  
hydroxy; lower alkoxy, including methoxy, ethoxy, and  
the like; lower alkyl; amino; lower alkylamino;  
diloweralkylamino; aryloxy (such as phenoxy);  
mercapto; mercapto lower alkyl; disulfide; lower  
30 alkylthio; and the like. One skilled in the art will

1 appreciate that the aforesaid substituents may have  
electron donating properties under one set of  
circumstances and electron withdrawing properties  
under different chemical conditions or circumstances;  
5 these are also contemplated to be within the scope of  
these terms. Moreover, the present invention  
contemplates any combination of substituents selected  
from the above-identified terms.

The term "lower alkanoyl" refers to a lower  
10 alkyl group in which a methylene group is replaced by  
a carbonyl (C), or in which a carbonyl group bridges



the main chain of formula I with lower alkyl or in  
15 which a lower alkyl group bridges a formyl group  
(-C-H) to the main chain of Formula I. Examples



include acetyl, propionyl, and the like.

20 "Lower alkoxy" denotes an alkyl group which  
is bridged to the main chain of Formula I by an O.  
Examples include methoxy, ethoxy, propoxy, and the  
like.

"Lower carbalkoxy" refers to a group of the  
25  $\begin{array}{c} \text{O} \\ \parallel \\ \text{C-O-} \end{array}$  (lower alkyl), wherein lower alkyl is  
defined herein above.

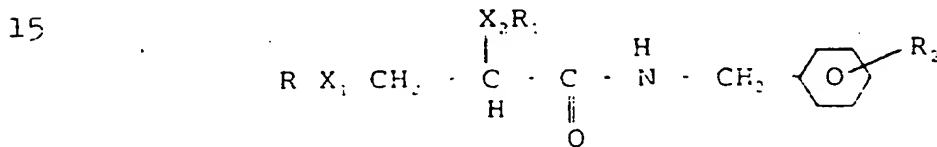
It is preferred that X<sub>1</sub> is O, S or NH. It  
is also preferred X<sub>2</sub> is O, S or NH. It is more  
30

1 preferred that at least one of  $X_1$  and  $X_2$  is O or S, and  
 even more preferable that  $X_1$  and  $X_2$  are independently O  
 or S. It is especially preferred that  $X_1$  and  $X_2$  are  
 the same. It is even more preferred that one of  $X_1$  and  
 5  $X_2$  is O. It is most preferred that  $X_1$  and  $X_2$  are both  
 O.

The preferred values of R and  $R_1$  are  
 independently lower alkyl. It is most preferred that  
 R and  $R_1$  are the same. The most preferred values of R  
 10 and  $R_1$  are methyl.

The preferred value of  $R_1$  is methyl and  
 especially hydrogen.

A preferred embodiment of the present  
 invention has the formula:



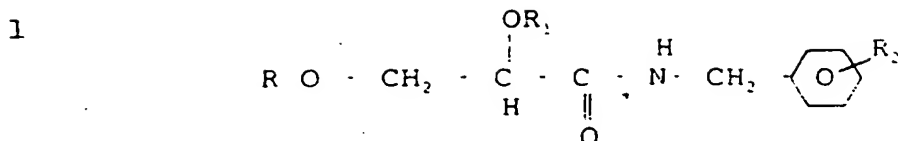
wherein R,  $X_1$ ,  $X_2$ , and  $R_1$  are as defined hereinabove  
 and  $R_2$  is hydrogen, an electron withdrawing group or  
 20 an electron donating group.

It is preferred that  $R_2$  is hydrogen, lower  
 alkyl or an electron withdrawing group, especially  
 halo. It is even more preferred that  $R_2$  is fluoro and  
 especially hydrogen. The more preferred  $X_1$ ,  $X_2$ , R and  
 25  $R_1$  are as described hereinabove.

A more preferred embodiment of the present  
 invention has the formula:

30

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5 wherein R, R<sub>1</sub> and R<sub>2</sub> are as defined herein. It is preferred that R and R<sub>1</sub> are the same. The more preferred R and R<sub>1</sub> groups are lower alkyl. It is most preferred that R and R<sub>1</sub> group are both methyl. The preferred values of R<sub>2</sub> are as defined hereinabove.

10 The compounds of the present invention contain at least one asymmetric carbon at the position α to the acyl group (C). As a result, the compounds of

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \end{array}$$

15 the present invention can exist in at least two stereoisomeric forms around this asymmetric carbon, the R and the S stereoisomer. Both stereoisomers as well as mixtures thereof, including racemic mixtures, are contemplated by the present invention. Additional  
20 asymmetric centers may exist in the side chains; the various stereoisomers, and mixtures thereof, including racemic mixtures, are contemplated by the present invention.

It is preferred that the compounds of the  
25 present invention be substantially pure, i.e., substantially free from impurities. It is most preferred that the compounds of the present invention be at least 75% pure (w/w) and more preferably greater than 90% pure (w/w) and most preferably greater than  
30 about 95% pure (w/w).

1           In a preferred embodiment of the present  
invention, the compounds of the present invention are  
enantiomerically pure, i.e., present in substantially  
one isomeric form, e.g., substantially the R  
5 stereoisomer (or the corresponding S stereoisomer)  
around the asymmetric carbon that is alpha to the acyl  
group in the compound of Formula I.

          It is to be understood that all combinations  
and permutations of the various Markush groups for the  
10 different variables are contemplated by the present  
invention. In addition, the various stereoisomers  
generated therefrom is also contemplated to be within  
the scope of the present invention.

          The compounds of the present invention are  
15 prepared by art recognized techniques from  
commercially available starting materials. Exemplary  
procedure for making the compounds of the present  
invention are outlined hereinbelow.

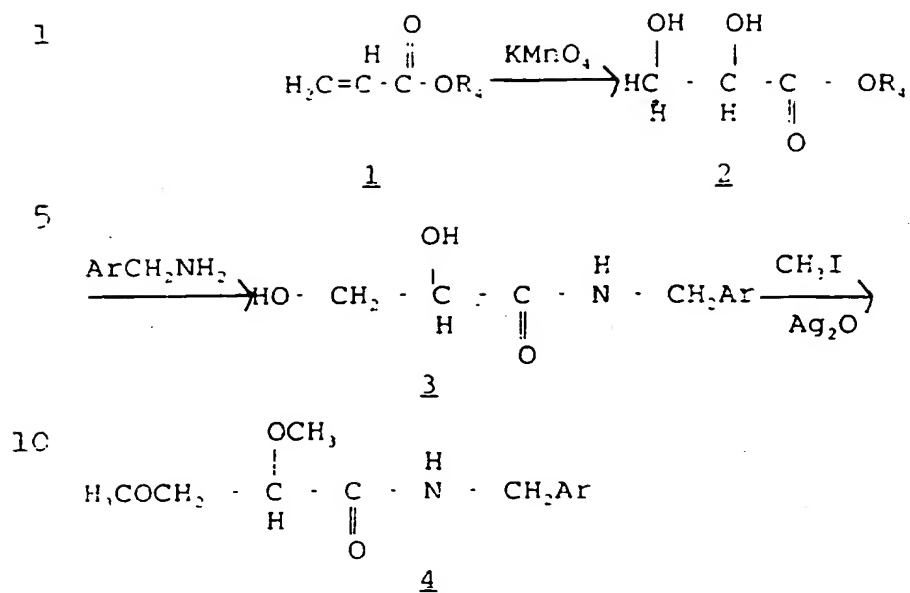
          When  $X_1$  and  $X_2$  are both O and R and  $R_1$  are both the  
20 same, the following scheme is exemplary:

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wherein

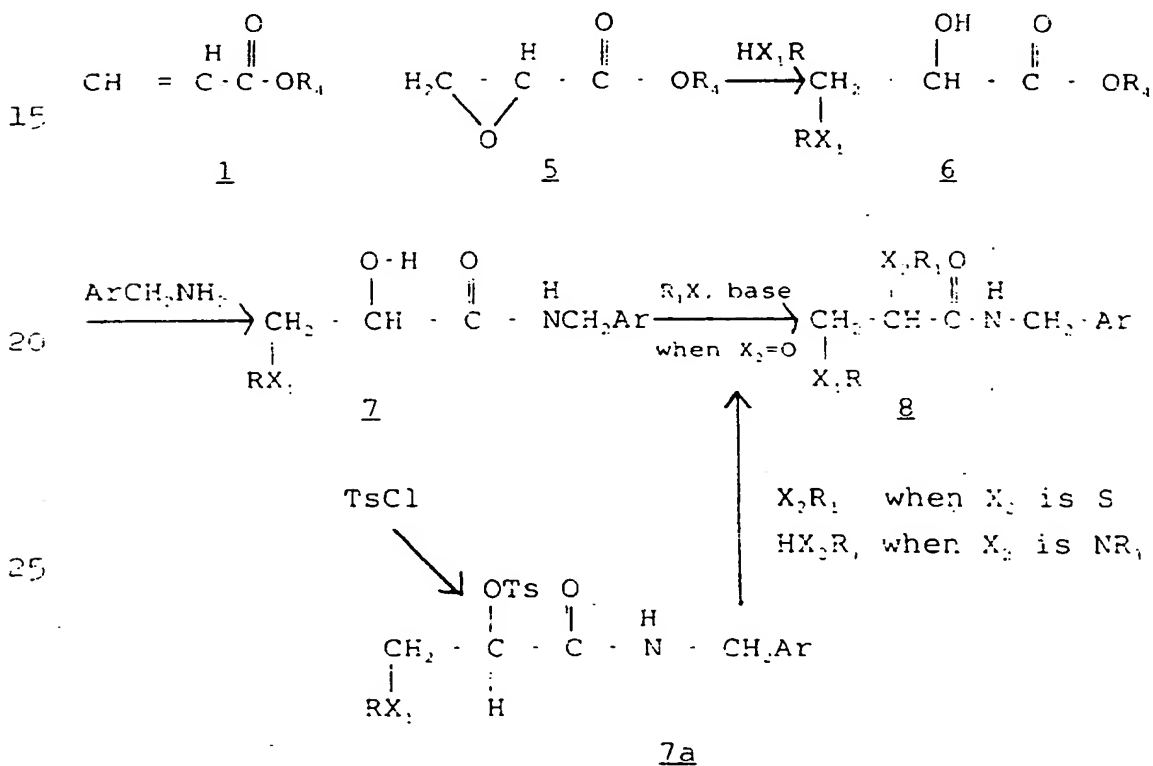
15  $R = R_1$

R<sub>1</sub> = lower alkyl, such as ethyl, methyl; or arylalkyl, such as benzyl.

SCHEME 1

Hydroxylation of an ester of acrylic acid (1) using oxidizing agents known in the art, such as alkaline  $\text{KMnO}_4$ ,  $\text{OsO}_4$ , and the like, provides the diol (2). The product 2 next undergoes an acylation reaction with  $\text{ArCH}_2\text{NH}_2$  to form the corresponding amide (3). The product 3 is converted to the diether (4) under Williamson reaction conditions, i.e., 3 is reacted with  $\text{RX}$ , wherein  $\text{R}$  is as defined herein, such as methyl and  $\text{X}$  is a good leaving group, such as OTs, OMs, halide or the like in the presence of base e.g., ( $\text{Ag}_2\text{O}$ ) to form the product 4.

Another more general procedure is as follows:



SCHEME 2

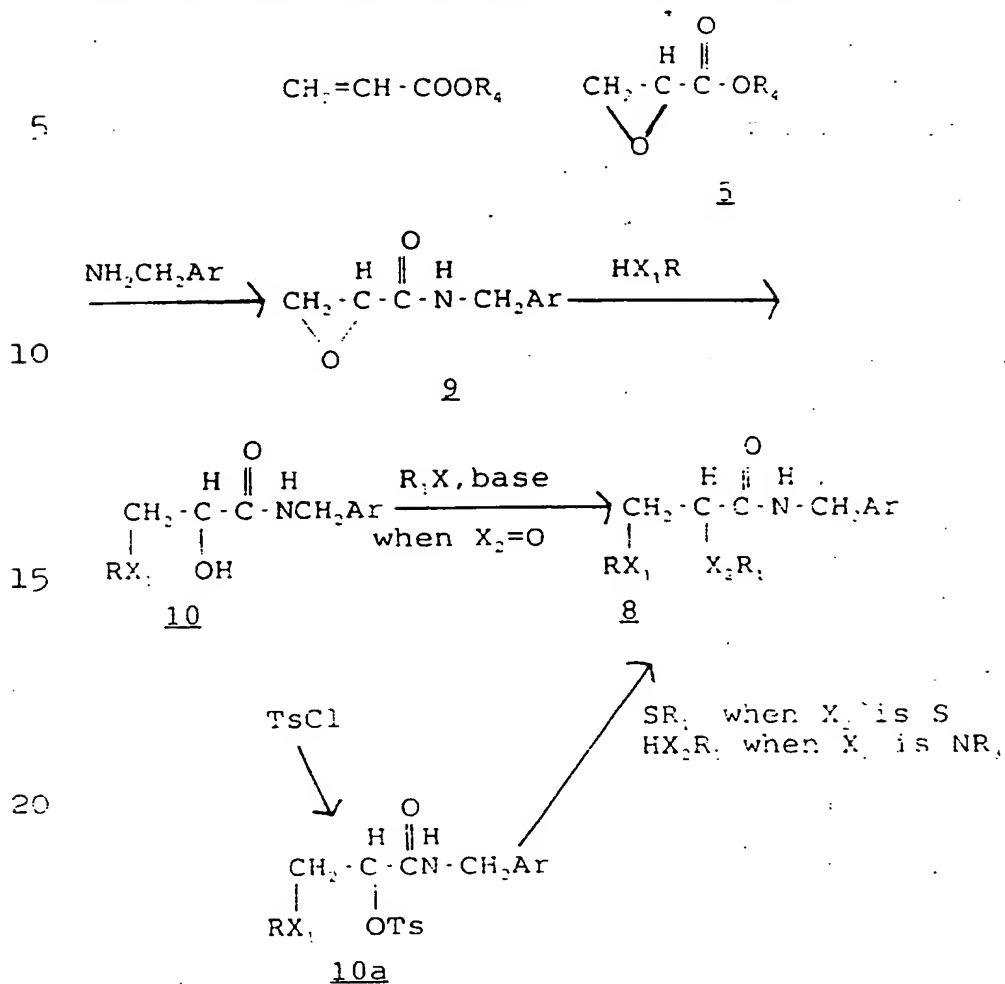
1           (5) is prepared by art recognized  
techniques. The epoxide (5) is formed by reacting 1  
(the ester of acrylic acid) with a peracid such as m-  
chloroperbenzoic acid, under Prilezhaev conditions.  
5 Other peracids, such as peracetic acid, perbenzoic  
acid, trifluoroperacetic acid, 3, 5-di-  
nitroperoxybenzoic acid may also be utilized.

          The epoxide (5) is reacted with  $HX_1R$  under  
basic or neutral conditions; under these conditions  
10 the ring opens up with the less substituted carbon  
being attacked by the reagent  $HX_1R$  to form the product  
(6). The product (6) is then reacted with  $ArCH_2NH_2$   
under amide forming conditions to form the amide (7).  
To form the ether (8), the amide (7) is reacted with  
15  $R_1X$ , where X is a good leaving group, such as  
mesylate, tosylate or halide in the presence of base  
under Williamson reaction conditions. However, if  $X_2$   
is S or  $NR_1$ , it is preferable to first convert the  
hydroxy group to a more reactive intermediate, such as  
20 the tosylate or mesylate by reacting 7 with  $TsCl$  (or  
 $MsCl$ ) to form the corresponding tosylate 7a (or  
mesylate) which is then reacted with  $R_1S'$  under  
nucleophilic conditions to form the corresponding  
thioether or  $HNR_1R_2$  under alkylation conditions to form  
25 the corresponding amine.

30

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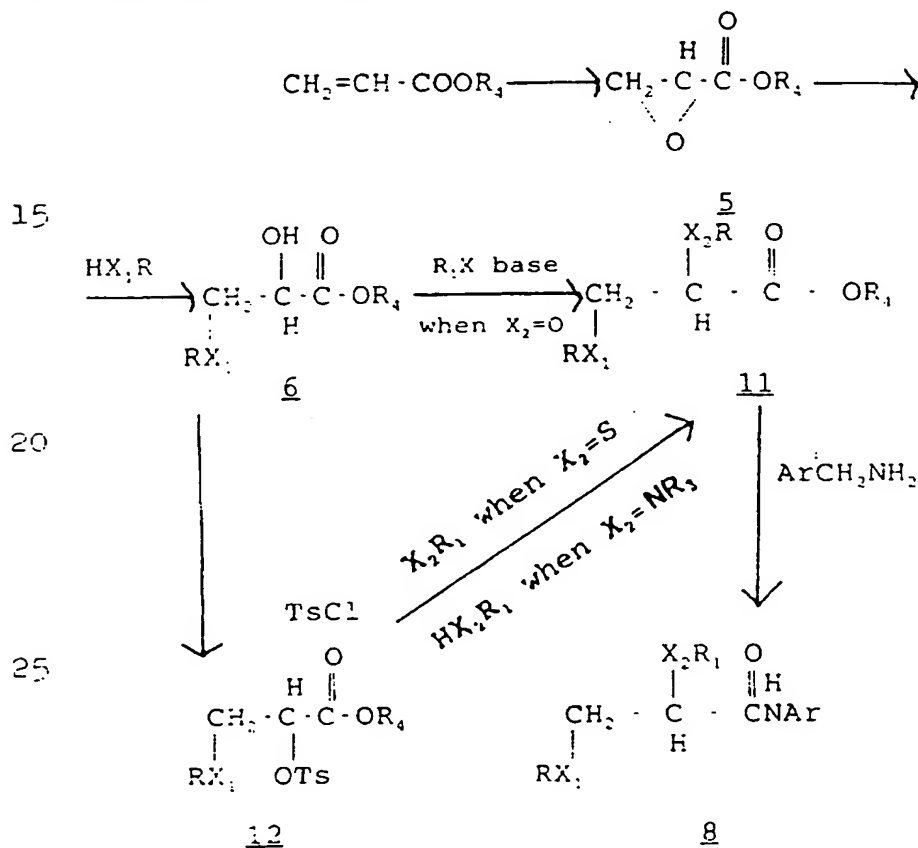
1 In a variation thereof, amide formation may  
 proceed the epoxide opening as follows:



SCHEME 2A

1 In this variation, the epoxide (5) is formed  
 from acrylic acid ester by reacting it with a peracid  
 such as that described hereinabove. Then 5 is reacted  
 with  $\text{NH}_2\text{CH}_2\text{Ar}$  under amide forming conditions to form  
 5 the corresponding amide (9). 9 is then reacted with  
 $\text{H}_1\text{XR}$  under neutral or basic conditions to form 10,  
 which is then converted to 8 under the conditions  
 discussed hereinabove in Scheme 2.

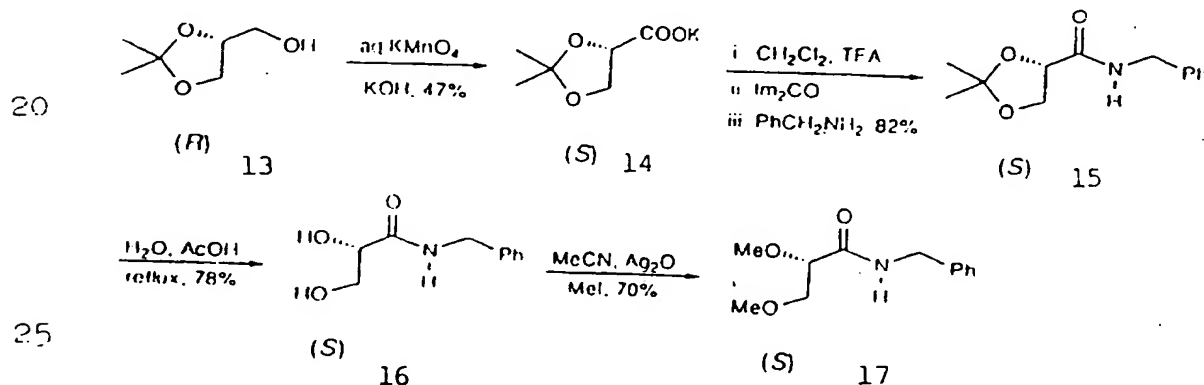
In another variation, the amide is formed  
 10 last as indicated hereinbelow:



SCHEME 2B

1           The ester of acrylic acid is converted to  
 the corresponding epoxide, which is then reacted with  
 HX<sub>2</sub>R as in Scheme 2 to form the corresponding alcohol  
 6. 6 is then converted to 11 by reacting it with  
 5 alkyl halide and base under Williamson reaction  
 conditions to form the corresponding ether.  
 Alternatively, the OH group in 6 is converted to a  
 more reactive group, such as by reacting 6 with mesyl  
 chloride or tosyl chloride to form 12 and the product  
 10 12 is reacted with X<sub>2</sub>R<sub>1</sub> when X<sub>2</sub> is S or HX<sub>2</sub>R<sub>1</sub> when X<sub>2</sub> is  
 NR<sub>1</sub> under nucleophile reaction conditions or  
 alkylation conditions, respectively to form (11). 11  
 is reacted with ArCH<sub>2</sub>NH<sub>2</sub> under amide forming conditions  
 to form 8.

15           Another variation depicted for X<sub>1</sub> and X<sub>2</sub>  
 being oxygen is indicated hereinbelow.



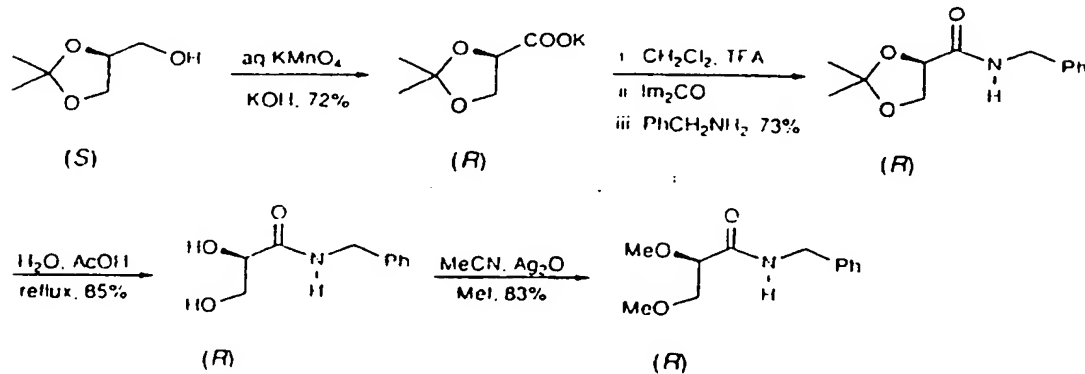
30           SCHEME 3

1 (R) (-)-2,2-dimethyl-1,3-dioxolane-4-methanol,  
 which is commercially available, is oxidized with an  
 oxidizing agent, such as potassium permanganate to form  
 the corresponding acid salt (14). 14 is then reacted  
 5 with  $\text{ArCH}_2\text{NH}_2$  under amide forming conditions to form the  
 corresponding amide acetal (15). Acid hydrolysis of  
 the acetal (15) forms the corresponding diol 16 which  
 is then reacted with alkyl halide in the presence of  
 base under Williamson reaction conditions to form the  
 10 corresponding diether.

The enantiomer of 17 is synthesized by  
 starting with S-(+)-2,2-dimethyl-1,3-dioxolane-4-  
 methanol, and following the procedure indicated  
 hereinabove, as shown in Scheme 4.

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SCHEME 4

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In the above schemes, R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, X, X<sub>1</sub>, X<sub>2</sub>, and Ar are as defined hereinabove.

The various substituents in the final products, e.g., on R, R<sub>1</sub>, R<sub>2</sub> and Ar may be present in the starting compounds, added to any of the intermediates or added after formation of the final products by known methods of substitution or conversion reactions. For example, the nitro groups can be added to the aromatic ring by nitration, and the nitro groups can be converted to other groups, such as amine by reduction; halo by diazotization of the amino group and then replacement by cuprous halide under Sandmeyer reaction conditions. Alternatively, replacement of the diazonium group by reacting the diazonium salt with fluoroboric acid, HBF<sub>4</sub>, followed by heating forms the corresponding fluoride. The alkanoyl group can be substituted onto the aryl groups by Friedel Crafts acylation. The alkanoyl groups can then be transformed to the corresponding alkyl groups by various methods, including Wolff-Kishner reduction and Clemmenson reduction. Amino groups can be alkylated to form mono- or dialkylamino groups and mercapto and hydroxy groups can be alkylated to form corresponding thioethers and ethers, respectively. Primary alcohols can be oxidized by oxidizing agents known in the art to form carboxylic acids or aldehydes and secondary alcohols can be oxidized to form ketones. Thus, substitutions or alteration reactions can be employed to provide a variety of substituents

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1 throughout the molecule of the starting material,  
intermediates or the final product.

In the above reactions, if the substituents  
themselves are reactive, then the substituents can  
5 themselves be protected according to the techniques  
known in the art. A variety of protecting groups  
known in the art may be employed. Examples of many of  
these groups may be found in Protective Groups in  
Organic Syntheses, by T.W. Greene, John Wiley and  
10 Sons, (1981), the contents of which are incorporated  
by reference.

Resulting mixtures of isomers are separated  
into purer isomers by methods known to one skilled in  
the art, e.g., by fractional distillation,  
15 crystallization chromatography, combination of these  
techniques and the like.

The present compounds exist in  
stereoisomeric forms, and the products obtained thus  
can be mixtures of the isomers, which are resolved by  
20 art recognized techniques. For example, racemic  
products can be resolved into optical antipodes by  
fractional crystallization, by the use of chiral  
stationery phase chromatography (HPLC) and the like.  
For a discussion of chiral stationary phase for HPLC,  
25 See DeCamp, Chirality, 1, 2-6 (1989), the contents of  
which are incorporated herein by reference.

The compounds of the present invention  
exhibit excellent anticonvulsant activity when  
administered in amounts ranging from about 0.5 mg to  
30 about 100 mg per kilogram of body weight per day. A

1 preferred dosage regimen ranges from about 10 mg per  
kilogram per day to about 50 mg per kilogram per day.  
This dosage regime may be adjusted by the physician to  
provide the optimum therapeutic response. For  
5 example, several divided doses may be administered  
daily or the dose may be proportionally reduced as  
indicated by the exigencies of the therapeutic  
situation. A decided practical advantage is that the  
active compound may be administered in an convenient  
10 manner such as by the oral, intravenous (where water-  
soluble), intramuscular or subcutaneous routes.

The active compound may be orally  
administered, for example, with an inert diluent or  
with an assimilable edible carrier, or it may be  
15 enclosed in hard or soft shell gelatine capsules, or  
it may be compressed into tablets, or it may be  
incorporated directly into the food of the diet. For  
oral therapeutic administration, the active compound  
may be incorporated with excipients and used in the  
20 form of ingestible tablets, buccal tablets, troches,  
capsules, elixirs, suspensions, syrups, wafers, and  
the like. Such compositions and preparations should  
contain at least 1% of active compound. The  
percentage of the compositions and preparations may,  
25 of course, be varied and may conveniently be between  
about 5 to about 80% of the weight of the unit. The  
amount of active compound in such therapeutically  
useful compositions is such that a suitable dosage  
will be obtained. Preferred compositions or  
30 preparations according to the present invention are

1 prepared so that an oral dosage unit form contains  
between about 5 and 1000 mg of active compound.

5 The tablets, trochès, pills, capsules and  
the like may also contain the following: A binder  
such as gum tragacanth, acacia, corn starch or  
gelatin; excipients such as dicalcium phosphate; a  
disintegrating agent such as corn starch, potato  
10 starch, alginic acid and the like; a lubricant such as  
magnesium stearate; and a sweetening agent such as  
sucrose, lactose or saccharin may be added or a  
flavoring agent such as peppermint, oil of  
wintergreen, or cherry flavoring. When the dosage  
unit form is a capsule, it may contain, in addition to  
materials of the above type, a liquid carrier.  
15 Various other materials may be present as coatings or  
to otherwise modify the physical form of the dosage  
unit. For instance, tablets, pills, or capsules may  
be coated with shellac, sugar or both. A syrup or  
elixir may contain the active compound, sucrose as a  
20 sweetening agent, methyl and propylparabens as  
preservatives, a dye and flavoring such as cherry or  
orange flavor. Of course, any material used in  
preparing any dosage unit form should be  
pharmaceutically pure and substantially non-toxic in  
25 the amounts employed. In addition, the active  
compound may be incorporated into sustained-release  
preparations and formulations. For example, sustained  
release dosage forms are contemplated wherein the  
active ingredient is bound to an ion exchange resin  
30 which, optionally, can be coated with a diffusion

1 barrier coating to modify the release properties of  
the resin.

The active compound may also be administered  
parenterally or intraperitoneally. Dispersions can  
5 also be prepared in glycerol, liquid polyethylene  
glycols, and mixture thereof and in oils. Under  
ordinary conditions of storage and use, these  
preparations contain a preservative to prevent the  
growth of microorganisms.

10 The pharmaceutical forms suitable for  
injectable use include sterile aqueous solutions  
(where water-soluble) or dispersions and sterile  
powders for the extemporaneous preparation of sterile  
injectable solutions or dispersions. In all cases the  
15 form must be sterile and must be fluid to the extent  
that easy syringability exists. It must be stable  
under the conditions of manufacture and storage and  
must be preserved against the contaminating action of  
microorganisms such as bacteria and fungi. The  
20 carrier can be a solvent or dispersion medium  
containing, for example, water, ethanol, polyol (for  
example, glycerol, propylene glycol, and liquid  
polyethylene glycol, and the like), suitable mixtures  
thereof, and vegetable oils. The proper fluidity can  
25 be maintained, for example, by the use of a coating  
such as lecithin, by the maintenance of the required  
particle size in the case of dispersions and by the  
use of surfactants. The prevention of the action of  
microorganisms can be brought about by various  
30 antibacterial and antifungal agents, for example,

1 parabens, chlorobutanol, phenol, sorbic acid,  
thimerosal, and the like. In many cases, it will be  
preferable to include isotonic agents, for example,  
sugars or sodium chloride. Prolonged absorption of  
5 the injectable compositions can be brought about by  
the use in the compositions of agents delaying  
absorption, for example; aluminum monostearate and  
gelatin.

Sterile injectable solutions are prepared by  
10 incorporating the active compound in the required  
amount in the appropriate solvent with various of the  
other ingredients enumerated above, as required,  
followed by filtered sterilization. Generally,  
dispersions are prepared by incorporating the various  
15 sterilized active ingredient into a sterile vehicle  
which contains the basic dispersion medium and the  
required other ingredients from those enumerated  
above. In the case of sterile powders for the  
preparation of sterile injectable solutions, the  
20 preferred methods are vacuum drying and the freeze-  
drying technique which yield a powder of the active  
ingredient plus any additional desired ingredient from  
previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable  
25 carrier" includes any and all solvents, dispersion  
media, coatings, antibacterial and antifungal agents,  
isotonic and absorption delaying agents, and the like.  
The use of such media and agents for pharmaceutical  
active substances is well known in the art. Except  
30 insofar as any conventional media or agent is

1 incompatible with the active ingredient, its use in  
the therapeutic compositions is contemplated.  
Supplementary active ingredients can also be  
incorporated into the compositions.

5 It is especially advantageous to formulate  
parental compositions in dosage unit form for ease of  
administration and uniformity of dosage. Dosage unit  
form as used herein refers to physically discrete  
units suited as unitary dosages for the mammalian  
10 subjects to be treated, each unit containing a  
predetermined quantity of active material calculated  
to produce the desired therapeutic effect in  
association with the required pharmaceutical carrier.  
The specifics for the novel dosage unit forms of the  
15 invention are dictated by and directly dependent on  
(a) the unique characteristics of the active material  
and the particular therapeutic effect to be achieved,  
and (b) the limitations inherent in the art of  
compounding such an active material for the treatment  
20 of disease in living subjects having a diseased  
conditions in which bodily health is impaired as  
herein disclosed in detail.

The principal active ingredient is  
compounded for convenient and effective administration  
25 in effective amounts with a suitable pharmaceutically  
acceptable carrier in dosage unit form as hereinbefore  
described. A unit dosage form can, for example,  
contain the principal active compound in amounts  
ranging from about 5 to about 1000 mg. Expressed in  
30 proportions, the active compound is generally present

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1 in from about 1 to about 750 mg/ml of carrier. In the  
case of compositions containing supplementary active  
ingredients, the dosages are determined by reference  
to the usual dose and manner of administration of the  
5 said ingredients.

Unless indicated to the contrary,  
percentages are by weight.

For a better understanding of the present  
invention reference is made to the following  
10 description and examples.

#### GENERAL METHODS

Melting points were determined with a  
15 Thomas-Hoover melting point apparatus and are  
uncorrected. Infrared spectra (IR) were run on a ATI  
Mattson Genesis Series FTIR™ spectrometer. Absorption  
values are expressed in wave-numbers ( $\text{cm}^{-1}$ ). Proton  
( $^1\text{H}$  NMR) and carbon ( $^{13}\text{C}$  NMR) nuclear magnetic  
20 resonance spectra were taken on a General Electric QE-  
300 NMR instrument. Chemical shifts ( $\delta$ ) are in parts  
per million (ppm) relative to tetramethylsilane and  
couplings constants (J values) are in Hertz. Low  
resolution mass spectra (CI+) were obtained with a  
25 Varian MAT CH-5 spectrometer by Dr. M. Moini at the  
University of Texas-Austin. The high-resolution  
chemical ionization mass spectrum was performed on a  
Finnigan MAT TSQ-70 by Dr. M. Moini at the University  
of Texas-Austin. Microanalyses were provided by  
30 Atlantic Microlab. Inc. (Norcross, GA). Thin-layer

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1 chromatography was performed on precoated silica gel  
GHLF microscope slides (2.5 x 10 cm; Analtech No.  
21521).

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### EXAMPLE 1

PREPARATION OF N-BENZYL 2,3-DIMETHOXY PROPIONAMIDE

### A. Ethylglycerate

5 KMnO<sub>4</sub> (15.65 g, .99 mmol) was dissolved in H<sub>2</sub>O  
(150 mL) and acetone (300 mL) and then cooled to  
-78°C. Ethyl acrylate (9.75 mL, 90 mmol) was slowly  
added with stirring at -78°C, and then the reaction  
mixture was allowed to warm up to 0°C. The inorganic  
10 salts were removed by filtration and washed with  
acetone (150 mL). The combined filtrates were  
concentrated under reduced pressure at temperatures  
below 40°C. The product was extracted using EtOAc (3  
x 200 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and then the solvent was  
15 removed under reduced pressure to afford the above-  
identified product as a white oil (6.70 g, 56%): R<sub>f</sub>  
0.60 (30% MeOH-CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.32 (t, J=7.2  
Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.31 (br s, OH), 3.27 (br s, OH), 3.85  
(dd, J=3.0, 11.7 Hz, CHH'OH), 3.91 (dd, J=3.3, 11.7  
20 Hz, CHH'OH), 4.25-4.27 (m, CH), 4.29 (q, J=7.2 Hz,  
OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 13.6 (OCH<sub>2</sub>CH<sub>3</sub>), 61.1 (OCH<sub>2</sub>CH<sub>3</sub>),  
63.7 (CH<sub>2</sub>OH), 71.6 (CHOH), 172.5 (C(O)) ppm.

### B. N-Benzyl 2,3-Dihydroxypropionamide

25 To the product of A (6.71 g, 50 mmol) was added benzylamine (5.74 mL, 100 mmol), and then the reaction solution was stirred at 100°C (18h). The excess benzylamine was removed in vacuo, and the residue triturated with CHCl<sub>3</sub> (100 mL) to solidify the  
30 product. The mixture was filtered to give the above

1 product as a white solid (6.30 g, 65%): mp 83-84°C; R<sub>f</sub>  
0.37 (10% MeOH-CHCl<sub>3</sub>); IR (KBr) 3408, 3294, 3033,  
2926, 1627, 1531, 1426, 1103, 1067, 730 cm<sup>-1</sup>; <sup>1</sup>H NMR  
(DMSO-d<sub>6</sub>) δ 3.40-3.51 (m, CHH'OH), 3.57-3.63 (m,  
5 CHH'OH), 3.89-3.94 (m, CHOH), 4.28 (d, J=6.3 Hz,  
CH<sub>2</sub>NH), 4.72 (t, J=5.7 Hz, CH<sub>2</sub>OH), 5.55 (d, J=5.4 Hz,  
CHOH), 7.12-7.32 (m, 5PhH), 8.22 (t, J=6.3 Hz, CH<sub>2</sub>NH);  
<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 41.7 (CH<sub>2</sub>NH), 63.9 (CH<sub>2</sub>OH), 73.1  
(CHOH), 126.6 (C<sub>4</sub>'), 127.1 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.1 (2C<sub>2</sub>'  
10 or 2C<sub>3</sub>'), 139.6 (C<sub>1</sub>'), 172.2 (C(O)) ppm; MS, (CI+) (rel  
intensity) 196 (M<sup>+</sup>+1, 100); M<sub>r</sub> (+Cl) 196.097 51 [M<sup>+</sup>+1]  
(calcd for C<sub>15</sub>H<sub>14</sub>NO, 196.097 37).

Anal Calcd for C<sub>15</sub>H<sub>14</sub>NO: C, 61.57; H, 6.71;  
N, 7.18. Found: C, 61.68; H, 6.76; N, 7.18.

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### C. N-Benzyl 2,3-Dimethoxypropionamide

Ag<sub>2</sub>O (9.27 g, 40 mmol) and MeI (4.98 mL, 80  
mmol) were added to room temperature to a stirred  
acetonitrile solution (50 mL) of the product of B  
20 (1.56 g, 8 mmol), and then the reaction mixture was  
stirred at room temperature (2d). The insoluble salts  
were filtered, and the solvent was removed in vacuo.  
The product was purified by flash column  
chromatography (EtOAc), and then further purified by  
25 distillation under reduced pressure (147°C/0.8 Torr)  
to give the above as a white oil (1.20 g, 67%): R<sub>f</sub>  
0.67 (5% MeOH-CHCl<sub>3</sub>); IR (KBr) 3419, 3319, 2931, 1661,  
1529 1454, 1131, 1108, 735, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ  
3.40 (br s, CH<sub>2</sub>OCH<sub>3</sub>), 3.48 (br s, CHOCH<sub>3</sub>), 3.70 (dd,  
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- 1 J=4.5, 10.5 Hz, CHH'OCH<sub>3</sub>), 3.79 (dd, J=2.4, 10.5 Hz, CHH'OCH<sub>3</sub>), 3.87 (dd, J=2.4, 4.5 Hz, CH), 4.50 (d, J=6.0 Hz, CH<sub>2</sub>NH), 6.98 (br s, CH<sub>2</sub>NH), 7.25-7.36 (m, 5PhH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 42.3 (CH<sub>2</sub>NH), 58.0 (CH<sub>2</sub>OCH<sub>3</sub> or CHOCH<sub>3</sub>), 58.7 (CH<sub>2</sub>OCH<sub>3</sub> or CHOCH<sub>3</sub>), 71.8 (CH<sub>2</sub>OCH<sub>3</sub>), 81.3 (CHOCH<sub>3</sub>), 126.8 (C<sub>4</sub>'), 126.9 (2C<sub>2</sub>' or 2C<sub>1</sub>'), 128.0 (2C<sub>3</sub>' or 2C<sub>3</sub>'), 137.7 (C<sub>1</sub>'), 169.4 (C(O)) ppm; MS, (CI+) (rel intensity) 224 (M<sup>+</sup>+1, 100); M<sub>r</sub> (+CI) 224.128 47 [M<sup>+</sup>+1] (calcd for C<sub>12</sub>H<sub>18</sub>NO<sub>3</sub>, 224.128 67).
- 5  
10 Anal Calcd for C<sub>12</sub>H<sub>18</sub>NO<sub>3</sub>: C, 62.91; H, 7.77; N, 6.11. Found: C, 63.12; H, 7.65; N, 6.09.
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EXAMPLE 2S-N-Benzyl-2,3-Dimethoxypropionamide

## A. Potassium (S)-2,2-dimethyl-1,3-dioxolane-4-carboxylate

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A solution of (R)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (2.00 g, 15 mmol) and KOH (0.90 g, 16 mmol) in H<sub>2</sub>O (60 ml) was cooled to 0°C and K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> (2.52 g, 16 mmol) was incrementally added. Upon addition, the reaction mixture was allowed to warm to room temperature, and then stirred for an additional 2 hours. The mixture was filtered through Celite and the clear filtrate was adjusted to pH 8.0 with 5% aqueous H<sub>2</sub>SO<sub>4</sub>. The resulting solution was evaporated in vacuo, and the white residue was suspended in boiling EtOH (100 ml) and filtered. Evaporation of the solvent gave the desired product as a white solid (1.3 g, 47%):  $[\alpha]_D^{25} = -28.2$  (c= 0.65, H<sub>2</sub>O).

## 20 B. (S)-N-Benzyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide.

The (S)-N-benzyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide was prepared as follows:

25 Potassium (S)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.86 g, 15.54 mmol) was suspended in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) under N<sub>2</sub>. Trifluoroacetic acid (1.77 g, 15.54 mmol) was then added, and the reaction stirred at room temperature for about 30 minutes. 1,1'-

30 Carbonyldiimidazole (2.60 g, 16 mmol) was then

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1 introduced at room temperature and the reaction was  
heated at reflux until CO<sub>2</sub> evolution ceased. The  
reaction mixture was cooled to room temperature and  
benzylamine (1.81 mL, 16.54 mmol) was added. The  
5 reaction was stirred for about 8 hours. The CH<sub>2</sub>CH<sub>2</sub>  
suspension was washed with water (2x25 mL) and the  
organic layer separated, dried (Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>) and evaporated  
in vacuo. The residue was purified by silica gel  
column chromatography (5% MeOH-CHCl<sub>3</sub>) to obtain the  
10 crude amide, which was then further purified by  
recrystallization from ethyl ether-petroleum ether to  
obtain 3.00 g (82%) of the desired product: mp 84-  
87°C; R<sub>f</sub> 0.70 (5% MeOH-CHCl<sub>3</sub>); [α]<sub>D</sub><sup>20</sup> = -17.2° (c=0.08,  
MeOH); IR (KBr) 3336, 1649, 1540, 1220, 1090, 735, 502  
15 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.39 (s, CCH<sub>3</sub>), 1.45 (s, CCH<sub>3</sub>),  
4.16 (dd, J=5.4, 9.0 Hz, OCHH'), 4.32 (dd, J= 7.6 Hz,  
OCHH'), 6.80-6.95 (m, NH), 7.20-7.41 (m, PhH); <sup>13</sup>C NMR  
(CDCl<sub>3</sub>) 25.0 (CCH<sub>3</sub>), 26.2 (CCH<sub>3</sub>), 42.9 (CH<sub>2</sub>Ph), 67.8  
(CH<sub>2</sub>), 75.1 (CH), 110.9 (C(CH<sub>3</sub>)<sub>2</sub>), 127.6 (2C<sub>2'</sub> or 2C<sub>3'</sub>  
20 and C<sub>3'</sub>), 128.8 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 137.9 (C<sub>1'</sub>), 171.2  
(C(O)) ppm; MS (+Cl) (rel. intensity) 236 (M<sup>+</sup>+1, 100),  
208(7), 178 (20); M<sub>r</sub> (+Cl) [M<sup>+</sup>+1] 236.128 44 (calcd for  
C<sub>11</sub>H<sub>18</sub>NO, 236.128 67); Anal. (C<sub>11</sub>H<sub>18</sub>NO<sub>3</sub>•0.25 H<sub>2</sub>O) C, H, N:

25 C. (S)-N-Benzyl-2,3-dihydroxypropionamide.

(S)-N-benzyl-2,3-dihydroxypropionamide was  
prepared in the following manner: (S)-N-benzyl-2,2-  
dimethyl-1,3-dioxolane-4-carboxamide (3.49 g, 14.8  
mmol) in a 50% aqueous acetic acid solution (86 mL)  
30 was heated at reflux (30 min). The solvent was

- 34 -

- 1 evaporated in vacuo, and the resulting residue was purified by silica gel column chromatography (10% MeOH-CHCl<sub>3</sub>) to obtain the desired product as a white solid (2.26 g, 78%); mp 83-84°C; R<sub>f</sub> 0.35 (10% MeOH-CHCl<sub>3</sub>);  $[\alpha]_D^{25} = -35.1^\circ$  (c=0.10, MeOH); IR (KBr) 3337, 1649, 1623, 1546, 1109, 1049, 971, 739, 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 3.45-3.59 (m, CHH'OH), 3.60-3.66 (m, CHH'OH), 3.90-3.98 (m, CHOH), 4.29 (d, J=6.3 Hz, CH<sub>2</sub>Ph), 4.65-4.85 (m, OH), 5.40-5.65 (m, OH), 7.15-7.40 (m, PhH), 8.25 (t, J=6.0 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 41.8 (CH<sub>2</sub>Ph), 64.1 (CH<sub>2</sub>OH), 73.2 (CHOH), 126.7 (C<sub>1</sub>'), 127.2 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.3 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 139.7 (C<sub>4</sub>'), 172.4 (C(O)NH) ppm; MS (+Cl) 196 (M<sup>+</sup>+1); M<sub>r</sub> (+Cl) 196.097 09 [M<sup>+</sup>+1] (calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>3</sub>, 196.097 37);
- 15 Anal (C<sub>10</sub>H<sub>11</sub>NO<sub>3</sub>) C, H, N.

#### D. (S)-N-Benzyl-2,3-dimethoxypropionamide.

- To an acetonitrile solution (74 mL) of (S)-N-benzyl-2,3-dihydroxypropionamide (2.26 g, 11.6 mmol), was added Ag<sub>2</sub>O (13.40 g, 58 mmol) and methyl iodide (7.4 mL, 116 mmol), and the resulting mixture was stirred at room temperature for 2 days. The salts were filtered, and the filtrate was evaporated in vacuo to obtain a clear oil which was purified by silica gel column chromatography (EtOAc) to give the above-identified product (1.89 g, 70%) as a clear oil; R<sub>f</sub> 0.43 (EtOAc);  $[\alpha]_D^{25} = -33.2^\circ$  (c=0.07, MeOH); IR (liquid film) 3324, 2931, 1667, 1528, 1455, 1108, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.41 (s, CH<sub>2</sub>OCH<sub>3</sub>), 3.49 (s, CHOCH<sub>3</sub>), 3.72 (dd, J=4.5, 10.5 Hz, CHH'OCH<sub>3</sub>), 3.80 (dd,

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- 1 J=27, 10.5 Hz, CHH'OCH<sub>3</sub>), 3.88 (dd, J=2.7, 4.5 Hz, CHOCH<sub>3</sub>), 4.51 (d, J=6.0 Hz, CH<sub>2</sub>Ph), 6.85-7.03 (m, NH), 7.25-7.38 (m, PhH), addition of excess (R)-mandelic acid gave only one signal for the CH<sub>2</sub>OCH<sub>3</sub> protons; <sup>13</sup>C
- 5 NMR (CDCl<sub>3</sub>) 42.8 (CH<sub>2</sub>Ph), 58.5 (CH<sub>2</sub>OCH<sub>3</sub>), 59.2 (CHOCH<sub>3</sub>), 72.2 (CH<sub>2</sub>OCH<sub>3</sub>), 81.7 (CHOCH<sub>3</sub>), 127.3 (C<sub>1</sub>'), 127.5 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.5 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 138.0 (C<sub>1</sub>'), 169.9 (C(O)NH) ppm; MS (+Cl) (rel. intensity) 224 (M'+1, 100), 222(11), 191(2); M<sub>r</sub>(+Cl) 224.129 29 {M'+1}
- 10 (calcd. for C<sub>12</sub>H<sub>18</sub>NO, 224.128 67); Anal (C<sub>12</sub>H<sub>17</sub>NO, •0.25 H<sub>2</sub>O) C, H, N.

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EXAMPLE 3

## (R)-N-Benzyl-2,3-dimethoxypropionamide

A. Potassium (R)-2,2-dimethyl-1,3-dioxolane-4-carboxylate.

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A solution of (S)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (2.00 g, 15 mmol) and KOH (0.90 g, 16 mmol) in H<sub>2</sub>O (60 mL) was cooled to 0° and KMnO<sub>4</sub> (2.52 g, 16 mmol) was incrementally added. Upon addition, the  
10 reaction mixture was allowed to warm to room temperature and then stirred for additional 2 hours. The mixture was filtered through Celite and the clear filtrate was adjusted to pH 8.0 with 5% aqueous H<sub>2</sub>SO<sub>4</sub>. The resulting solution was evaporated in vacuo, and  
15 the white residue was suspended in boiling EtOH (100 mL) and filtered. Evaporation of the solvent gave the desired product (2.00 g, 72%) as a white solid:  
[α]<sub>D</sub><sup>25</sup> = +29.5° (c=0.4, H<sub>2</sub>O) (lit. [α]<sub>D</sub><sup>25</sup> = +30.1° (c=1.03, H<sub>2</sub>O)).

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B. (R)-N-Benzyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide.

Potassium (R)-2,2-dimethyl-1,3-dioxolane-4-  
25 carboxylate (1.31 g, 7.1 mmol) was suspended in dry CH<sub>2</sub>Cl<sub>2</sub> (50mL) under N<sub>2</sub> and then trifluoroacetic acid (0.81 g, 7.1 mmol) was added and the reaction stirred at room temperature (30 min). 1.1'-  
Carbonyldiimidazole (1.15 g, 7.1 mmol) was then  
30 introduced at room temperature, and the reaction was

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1 heated at reflux until CO<sub>2</sub> evolution ceased. The  
reaction mixture was cooled to room temperature,  
benzylamine (0.78 mL, 7.1 mmol) was added and the  
reaction stirred (18 hours). The CH<sub>2</sub>Cl<sub>2</sub> suspension was  
5 washed with water (2x25 mL), and the organic layer  
separated, dried (Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>), and evaporated in vacuo.  
The residue was purified by silica gel column  
chromatography (5% MeOH-CHCl<sub>3</sub>) to obtain the crude  
amide, which was further purified by recrystallization  
10 from ethyl ether-petroleum ether to give the pure  
amide (1.22 g, 73%; R<sub>f</sub> 0.70 (5% MeOH-CHCl<sub>3</sub>; mp 81-84°C;  
[α]<sub>D</sub><sup>25</sup> = +17.1° (c = 0.08, MeOH); IR (KBr) 3336, 1649,  
1540, 1221, 1090, 735, 500 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.39  
(s, CCH<sub>3</sub>), 1.45 (s, CCH<sub>3</sub>), 4.16 (dd, J=5.4, 9.0 Hz,  
15 OCHH'), 4.32 (dd, J=7.4, 9.0 Hz, OCHH'), 4.49 (d,  
J=6.0 Hz, CH<sub>2</sub>Ph), 4.55 (dd, J=5.4, 7.4 Hz, OCH), 6.80-  
6.95 (m, NH), 7.23-7.41 (m, PhH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 25.1  
(CCH<sub>3</sub>), 26.3 (CCH<sub>3</sub>), 43.0 (CH<sub>2</sub>Ph), 67.9 (CH<sub>2</sub>), 75.2 (CH),  
111.0 (C(CH<sub>3</sub>)<sub>2</sub>), 127.7 (2C<sub>2'</sub> or 2C<sub>3'</sub> and C<sub>4'</sub>), 128.9  
20 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 137.9 (C<sub>1'</sub>), 171.3 (C(O)) ppm; MS(+Cl)  
(rel. intensity) 236 (M<sup>+</sup>+1, 100), 208(72), 178 (43); M<sub>r</sub>  
(+Cl) 236.128 99 [M<sup>+</sup>+1] (calcd. for C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub>); Anal  
(C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub>•0.5 H<sub>2</sub>O) C, H, N.

25 C. (R)-N-Benzyl-2,3-dihydroxypropionamide.

A 50% aqueous acetic acid solution (30 mL)  
containing (R)-N-benzyl-2,2-dimethyl-1,3-dioxolane-4-  
carboxamide (1.22 g, 5.19 mmol) was heated at reflux  
30 (30 min). The solvents were evaporated in vacuo and

1 the resulting residue was purified by silica gel  
column chromatography (10% MeOH-CHCl<sub>3</sub>) to obtain the  
desired product as a white solid (0.86 g, 85%); mp 83-  
84°C, R<sub>f</sub> 0.35 (10% MeOH-CHCl<sub>3</sub>);  $[\alpha]_D^{25} = +35.4^\circ$  (c=0.19,  
5 MeOH); IR (KBr) 3336, 1649, 1623, 1542, 1400, 1319,  
1110, 1049, 972, 739, 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  3.42-  
3.55 (m, CHH' OH), 3.53-3.64 (m, CHH' OH), 3.89-3.95  
(m, CHOH), 4.28 (d, J=6.0 Hz, CH<sub>2</sub>Ph), 4.74 (t, J=  
5.7 Hz, CH<sub>2</sub>OH), 5.57 (d, J=5.4 Hz, CHOH) 7.19-7.35 (m,  
10 PhH), 8.24 (t, J=6.0 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 41.7  
(CH<sub>2</sub>Ph), 64.0 (CH<sub>2</sub>OH), 73.1 (CHOH), 126.6 (C<sub>4</sub>'), 127.2  
(2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.2 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 139.6 (C<sub>1</sub>'), 172.2  
(C(O)NH) ppm; MS(+Cl) (rel. intensity) 196 (M<sup>+</sup>+1,  
100); M<sub>r</sub> (+Cl) 196.098 03 [M<sup>+</sup>+1] (calcd. for C<sub>13</sub>H<sub>13</sub>NO,  
15 196.097 37); Anal. (C<sub>13</sub>H<sub>13</sub>NO) C, H, N.

#### D. (R)-N-Benzyl-2,3-dimethoxypropionamide

To an acetonitrile solution (44 mL) of (R)-  
N-benzyl-2,3-dihydroxypropionamide (1.35 g, 6.94 mmol)  
20 was added Ag<sub>2</sub>O (8.05 g, 35 mmol) and methyl iodide  
(4.4 mL, 70 mmol), and then the mixture was stirred at  
room temperature (2 days). The salts were filtered,  
and the filtrate was evaporated in vacuo to obtain a  
clear oil which was purified by silica gel column  
25 chromatography (EtOAc) to give (R)-N-benzyl-2,3-  
dimethoxypropionamide (1.29 g, 83%) as a clear oil: R<sub>f</sub>  
0.43 (EtOAc);  $[\alpha]_D^{25} = +33.6^\circ$  (c=0.10 MeOH); IR (liq.  
film) 3320, 2930, 1662, 1528, 1455, 1107, 700 cm<sup>-1</sup>; <sup>1</sup>H  
NMR (CDCl<sub>3</sub>)  $\delta$  3.41 (s, CH<sub>2</sub>OCH<sub>3</sub>), 3.71 (dd, J=4.5, 10.5  
30 Hz, CHH'OCH<sub>3</sub>), 3.80 (dd, J=2.7, 10.5 Hz, CHH'OCH<sub>3</sub>).

- 39 -

- 1 3.88 (dd,  $J=2.7, 4.5$  Hz,  $\text{CHOCH}_3$ ), 4.51 (d,  $J=6.0$  Hz,  $\text{PhCH}_2$ ), 6.95-7.05 (m, NH), 7.28-7.40 (m, PhH); addition of excess (R)-mandelic acid gave only one signal for the  $\text{CH}_2\text{OCH}_3$  protons;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 43.0
- 5 (CH<sub>2</sub>Ph), 58.6 ( $\text{CH}_2\text{OCH}_3$ ), 59.4 ( $\text{CHOCH}_3$ ), 72.3 ( $\text{CH}_2\text{OCH}_3$ ), 81.8 (CH), 127.5 ( $\text{C}_4'$ ), 127.6 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 128.7 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 138.0 ( $\text{C}_1'$ ), 170.0 (C(O) ppm; MS (+Cl) rel. intensity) 224 ( $\text{M}^++1$ , 100), 119(3);  $\text{M}_r$  (+Cl) 224.127 99 [ $\text{M}^++1$ ] (calcd. for  $\text{C}_{12}\text{H}_{16}\text{NO}$ , 224.128 67);
- 10 Anal. ( $\text{C}_{12}\text{H}_{16}\text{NO} \cdot 0.15 \text{H}_2\text{O}$ ) C, H, N.

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1                                    PHARMACOLOGY

                  Compounds were screened under the auspices  
of the National Institutes of Health for  
anticonvulsant activity in male albino Cartworth Farms  
5 No. 1 mice (ip route). Activity was established using  
the electrical (maximal electroshock or MES) test. In  
the MES test, a drop of electrolyte solution with  
anesthetic (0.5% butacaine hemisulfate in 0.9% sodium  
chloride) was used in the eyes of the animals prior to  
10 positioning the corneal electrodes and delivery of  
current. A 60 cycle alternating current was  
administered for 0.2 sec. at 50 mA. Protection  
endpoints were defined as the abolition of the hind  
limb tonic extensor component of the induced seizure.  
15 In mice, the effects of compounds on forced  
spontaneous motor activity were determined using the  
rotorod test. The inability of animals to maintain  
their balance for 1 min. on a 1 inch diameter knurled  
rod at 6 rpms in 3 successive trials demonstrated  
20 motor impairment. Normally under these conditions, a  
mouse can maintain its balance almost indefinitely.  
In the mouse identification screening study all  
compounds were given at three dose levels (30, 100,  
300 mg/kg) and two time periods (0.5, 4h). Typically,  
25 in the MES seizures test one animal was used at 30  
mg/kg and 300 mg/kg, and three animals at 100 mg/kg.  
In the rotorod toxicity test four animals were used at  
30 mg/kg, and 300 mg/kg, and eight animals at 100  
mg/kg. If activity was found at 30 mg/kg, then lower  
30 dosages were used to find the ED<sub>50</sub> values.

1           The quantitative determination of the median  
effective ( $ED_{50}$ ) and toxic doses ( $TD_{50}$ ) were conducted  
at previously calculated times of peak effect. Groups  
of at least eight animals were tested using different  
5 doses of test compound until at least two points were  
determined between 100 and 0% protection and minimal  
motor impairment. The dose of candidate substance  
required to produce the defined endpoint in 50% of the  
animals in each test and the 95% confidence interval  
10 were calculated.

          The results of the compound of the example  
of the present invention was compared with N-Benzyl-  
2,3-dihydroxypropimamide and known anticonvulsants  
under the aforementioned tests, and the results are  
15 given in the table hereinbelow.

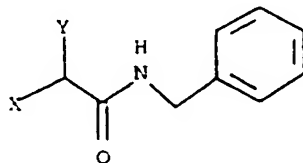
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**TABLE 1**  
**Pharmacological Data in Mice<sup>a</sup>**



Stereo-isomer	X	Y	mp <sup>b</sup>	MES <sup>c</sup> ED <sub>50</sub>	Tox <sup>d</sup> TD <sub>50</sub>	P.I. <sup>e</sup>
R, S	OCH <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	oil	30 [0.25; (17-43)]	280 [0.25] (240-300)	9.3
R, S	OH	CH <sub>2</sub> OH	83-84	>100, <300 [0.5]	>300	
R	OCH <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	oil	>30, <100 [0.5]	300 [0.5]	
S	OCH <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	oil	>30, <100 [0.5]	Not reported	
	phenytoin			6.5 [2; (5.7-7.2)]	43 [0.5] (36-48)	6.6
	phenobarbital			22 [1] (15-23)	69 [0.5] (63-73)	3.1
	valproate			290 [0.25] (240-360)	480 [0.25] (420-570)	1.7

<sup>a</sup> The compounds were administered intraperitoneally. ED<sub>50</sub> and TD<sub>50</sub> values are in mg/kg. Numbers in parentheses are 95% confidence intervals. A dose effect data for these compounds was obtained at the \*time of peak effect\* (indicated in hours in the brackets). The compounds were tested through the auspices of the National Institute of Neurological and Communicative Disorders and Stroke at the National Institutes of Health. <sup>b</sup>Melting points (°C) are uncorrected. <sup>c</sup>MES = maximal electroshock seizure test. <sup>d</sup>Neurologic toxicity determined using the rotorod test unless otherwise noted. <sup>e</sup>PI = protective index (TD<sub>50</sub>/ED<sub>50</sub>).

1           The results clearly show that the dihydroxy  
compound has very low anticonvulsant activity. On the  
other hand, the compounds of the present invention,  
e.g., N-Benzyl 2,3-Dimethoxypropionamide have much  
5 greater efficacy. In fact, the  $ED_{50}$  of the diether of  
the present invention is greater than 3 times more  
effective than that of the dihydroxy compound.  
Moreover, the P.I. of the diether of the present  
invention is greater than 3 times more effective than  
10 that of the dihydroxy compound.

          The data also illustrate that compounds of  
the present invention, such as N-Benzyl 2,3-  
dimethoxypropionamide, exhibit excellent drug  
profiles, as indicated by its unexpectedly high  
15 protective index. The protective index measures the  
relationship between the doses of a drug required to  
produce undesired and desired effects, respectively,  
and is measured as the ratio between the median toxic  
dose and the median effective dose ( $TD_{50}/ED_{50}$ ). As  
20 shown by the data, the diether has a P.I. of 9.3,  
which is significantly greater than the P.I. values of  
phenytoin, phenobarbital and valproate. Thus, the  
data clearly indicate that compounds of the present  
invention are excellent anticonvulsant drugs.

25           The above preferred embodiments and examples  
are given to illustrate the scope and spirit of the  
present invention. The embodiments and examples  
described herein will make apparent to those skilled  
in the art other embodiments and examples. These  
30 other embodiments and examples are within the

1 contemplation of the present invention. Therefore,  
the present invention should be limited only by the  
appended claims.

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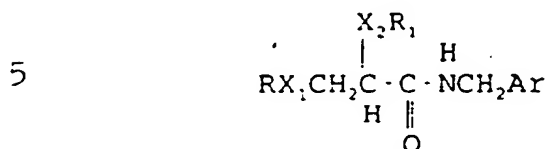
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1 WHAT IS CLAIMED:

1. A compound of the formula:



or pharmaceutically acceptable salts thereof wherein

10 Ar is aryl which is unsubstituted or substituted with at least one electron donating group or electron withdrawing group;

R and R<sub>1</sub> are independently lower alkyl, aryl, aryl lower alkyl, lower cycloalkyl or lower cycloalkyl lower alkyl, wherein R and R<sub>1</sub> groups are  
15 independently unsubstituted or substituted with at least one electron donating group or electron withdrawing group;

X<sub>1</sub> and X<sub>2</sub> are independently O, S, or NR, and R<sub>1</sub> is hydrogen or lower alkyl.

20 2. The compound according to Claim 1 wherein R and R<sub>1</sub> are the same.

3. The compound according to Claim 1 wherein X<sub>1</sub> and X<sub>2</sub> are the same.

4. The compound according to Claim 1  
25 wherein X<sub>1</sub> and X<sub>2</sub> are the same and R<sub>1</sub> and R are the same.

5. The compound according to Claim 1 wherein X<sub>1</sub> and X<sub>2</sub> are independently O, S, NH or NCH<sub>3</sub>.

6. The compound according to Claim 5  
30 wherein X<sub>1</sub> and X<sub>2</sub> are independently O or S.

1            7. The compound according to Claim 6  
wherein X<sub>1</sub> and X<sub>2</sub> are the same.

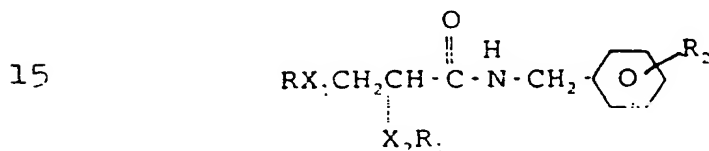
8. The compound according to Claim 6 wherein  $X_1$  and  $X_2$  are O.

5 9. The compound according to Claim 1  
wherein R and R<sub>1</sub> are independently lower alkyl.

10. The compound according to Claim 1 wherein R and R<sub>1</sub> are independently alkyl containing 1-3 carbon atoms.

10            11. The compound according to Claim 10  
wherein R and R<sub>1</sub> and methyl.

12. The compound according to Claim 1  
having the formula:



wherein

R and R<sub>1</sub> are independently lower alkyl, aryl, aryl lower alkyl, cycloalkyl or cycloalkyl lower alkyl, said R and R<sub>1</sub> groups being unsubstituted or substituted with an electron donating group or electron withdrawing group;

$X_1$  and  $X_2$  are independently O, S, or NR<sub>3</sub>;

R<sub>1</sub> is hydrogen or lower alkyl; and

25             $R_2$  is hydrogen, an electron donating group  
or an electron withdrawing group.

13. The compound according to Claim 12 wherein X<sub>1</sub> and X<sub>2</sub> are independently O, S, NH or NCH<sub>3</sub>.

14. The compound according to Claim 13 wherein R and R<sub>1</sub> are independently lower alkyl.
15. The compound according to Claim 12 wherein X<sub>1</sub> and X<sub>2</sub> are the same.
16. The compound according to Claim 13 wherein X<sub>1</sub> and X<sub>2</sub> are independently O or S.
17. The compound according to Claim 16 wherein X<sub>1</sub> and X<sub>2</sub> are both S or are both O.
18. The compound according to Claim 12 wherein R and R<sub>1</sub> are independently alkyl containing 1-3 carbon atoms.
19. The compound according to Claim 14 or 18 wherein R and R<sub>1</sub> are the same.
20. The compound according to Claim 12 of the formula
- $$\begin{array}{c}
 \text{OR}_1 \\
 | \\
 \text{ROCH}_2\text{CH}-\text{C}-\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-\text{R}_2 \\
 || \\
 \text{O}
 \end{array}$$
21. The compound according to Claim 20 wherein R and R<sub>1</sub> are independently lower alkyl.
22. The compound according to Claim 21 wherein R and R<sub>1</sub> are independently lower alkyl containing 1-3 carbon atoms.
23. The compound according to Claim 22 wherein R<sub>1</sub> and R are the same.
24. The compound according to Claim 20 which is N-Benzyl 2,3-dimethoxypropionamide.
25. A stereoisomer of the compound of Claim 1.

1                    26. A stereoisomer of the compound of Claim  
12.

27. A stereoisomer of the compound of Claim 20.

5 28. A stereoisomer of the compound of Claim  
24.

29. A pharmaceutical composition comprising an anticonvulsant effective amount of a compound according to any one of Claims 1, 12, 20 or 24 and a pharmaceutical carrier therefor.

30. A method of treating central nervous system disorders in an animal in need of such treatment comprising administering to said animal an anticonvulsant effective amount of a compound according to any one of Claims 1, 12, 20 or 24.

31. The method according to Claim 30 wherein said animal is a mammal.

32. The method according to Claim 31 wherein said mammal is human.

20 33. The method according to Claim 30 wherein the compound is administered in an amount ranging from about 0.5 to about 100 mg/kg of body weight per day.

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## INTERNATIONAL SEARCH REPORT

International Application No

PC1/US 97/17561

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C235/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 5 378 729 A (H. L. KOHN ET AL) 3 January 1995 cited in the application see claims 1,67	1,29
A	--- D. CHOI ET AL: "Synthesis and anticonvulsant activities of N-benzyl-2-acetamidopropionamide derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 9, 26 April 1996, pages 1907-1916, XP002052790 see page 1907: example 18; table 1 --- -/--	1,29

☒ Further documents are listed in the continuation of box C☒ Patent family members are listed in annex

## \* Special categories of cited documents

\* A\* document defining the general state of the art which is not considered to be of particular relevance

E\* earlier document, but published on or after the international filing date

L\* document which may throw doubts on priority claims; or which is cited to establish the publication date of another citation or other special reason (as specified)

O\* document referring to an oral disclosure, use, exhibition or other means

P\* document published prior to the international filing date but later than the priority date claimed

T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X\* document of particular relevance, the claimed invention cannot be considered novel; or cannot be considered to involve an inventive step when the document is taken alone

Y\* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z\* document, member of the same patent family

Date of the actual completion of the international search

21 January 1998

Date of making of the international search report

06.02.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2

NL - 2280 HV Rijswijk

Tel: +31-70-340-2040 Fax: +31-70-340-3016

Fax: +31-70-340-3016

Authorized officer:

Voyiazoglou, D

# INTERNATIONAL SEARCH REPORT

International Application No

PC1/US 97/17561

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P.X	<p>D.-CHOI ET AL : "The anticonvulsant activities of functionalized N-benzyl 2-acetamidoacetamides. The importance of the 2-acetamido substituent" BIOORGANIC &amp; MEDICINAL CHEMISTRY, vol. 4, no. 12, December 1996, pages 2105-2114, XP002052791 see example 21; table 2</p> <p>-----</p>	<p>1.20,24, 29</p>

# INTERNATIONAL SEARCH REPORT

International application No

PCT/US 97/ 17561

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

- 1 ☒ Claims Nos. 30-33  
because they relate to subject matter not required to be searched by this Authority, namely:  
They refer to a method for treatment of the animal/human body by therapy  
Rule 39.1(iv) PCT.
- 2 ☐ Claims Nos..  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful international Search can be carried out, specifically:
- 3 ☐ Claims Nos..  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest
- ☐ No protest accompanied the payment of additional search fees

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/17561

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE 3786865 T	09-12-93
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		DK 72686 A	16-08-86
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